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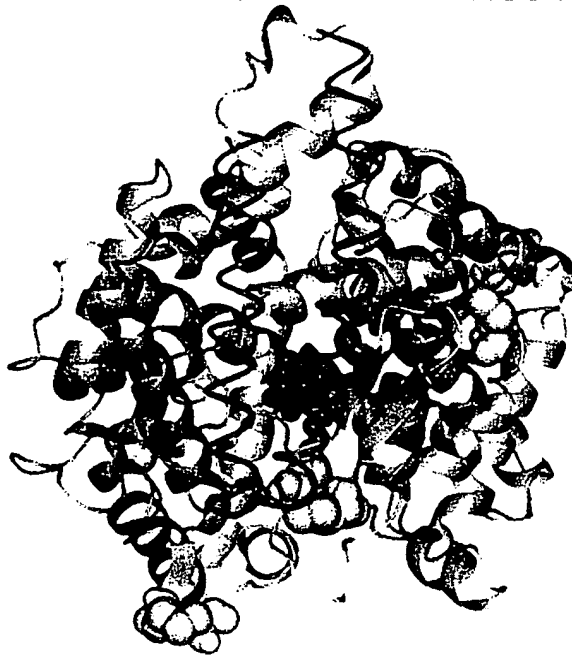
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Fig. 1. Testicular ACE [2]. Ribbon model of tACE with an inhibitor, lisinopril, bound to the active site (space-filling red, blue and green atoms). The lid formed by helices $\alpha 1$ and $\alpha 2$ is indicated as a thin blue wire above the active site. The 7 evolutionarily conserved cysteines are indicated in yellow. The 2 cystines with their associated short β -sheets are visible. The cystine on the right of the figure links helix $\alpha 17$ to helix H7. The side wall formed by $\beta 4$ and $\beta 5$ is next to the active site, as indicated by lisinopril.

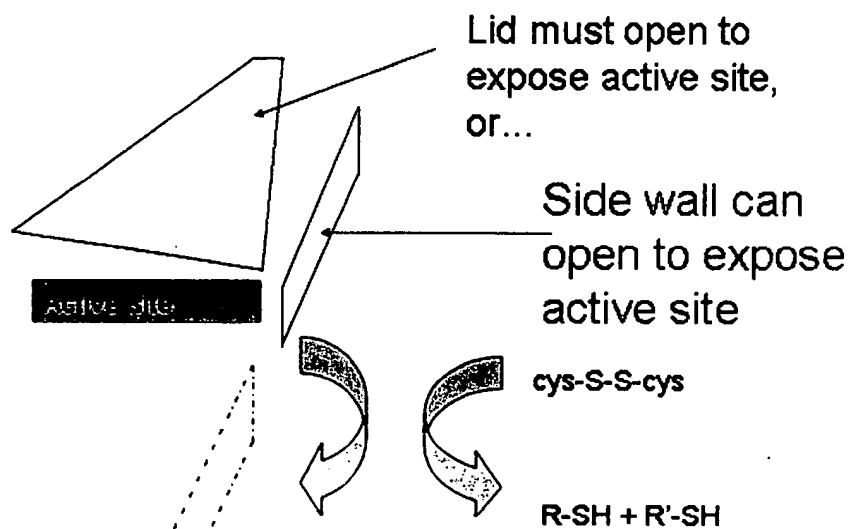
tACE: Natesh et al. Nature 421:551, 2003



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Fig. 2. Testicular ACE as redox- and mechanosensor.

tACE as redox sensor



Refs. Moskowitz et al, in press; Natesh et al, Nature 421:551, 2003

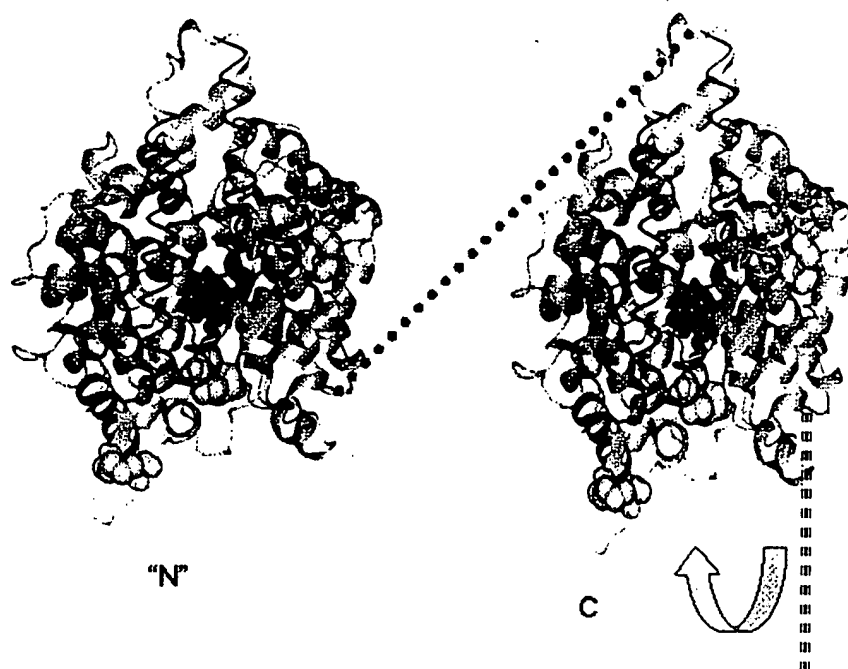
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Fig. 3. *In silico* reduction of tACE: conversion of one cysteine to an alanine. "Reduction" of the middle cystine of tACE removes a side wall of the active site. C352 and C370 in this drawing correspond to C383 and C401, respectively, in the numbering scheme of the tACE precursor (SwissProt P22966).



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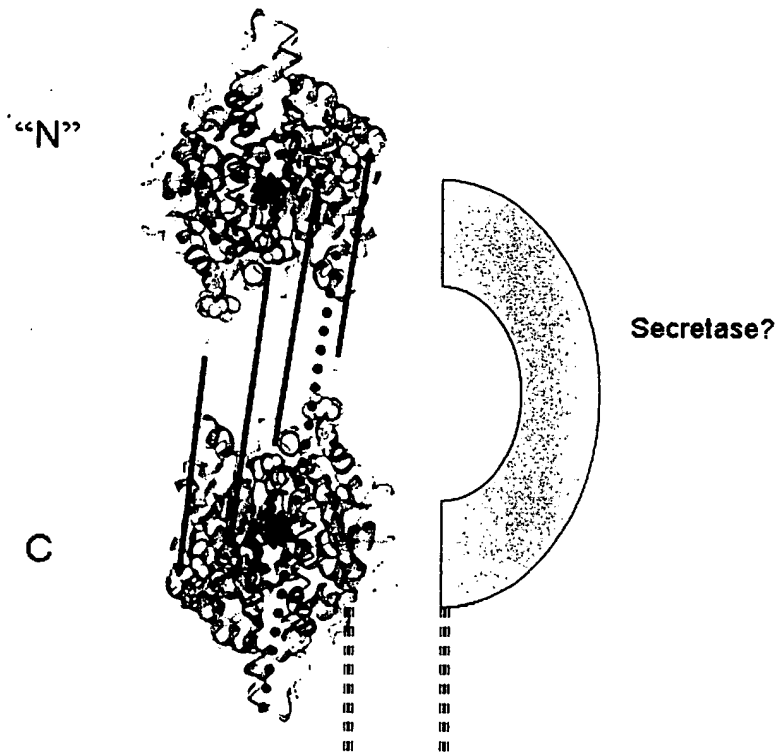
Fig. 4a. Somatic ACE (sACE).



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Fig. 4b. Somatic ACE showing complementarity of the N- and C-terminal domains. The secretase, an integral membrane protein associated with sACE, may have a chaperone-like function to hold the two domains of sACE together.

Note: "Tongue-in-groove" fit



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Figure 5. The "disulfide zipper" at the heart of sACE: a potential electron transport chain.

sACE: Dimerization via a Disulfide Zipper

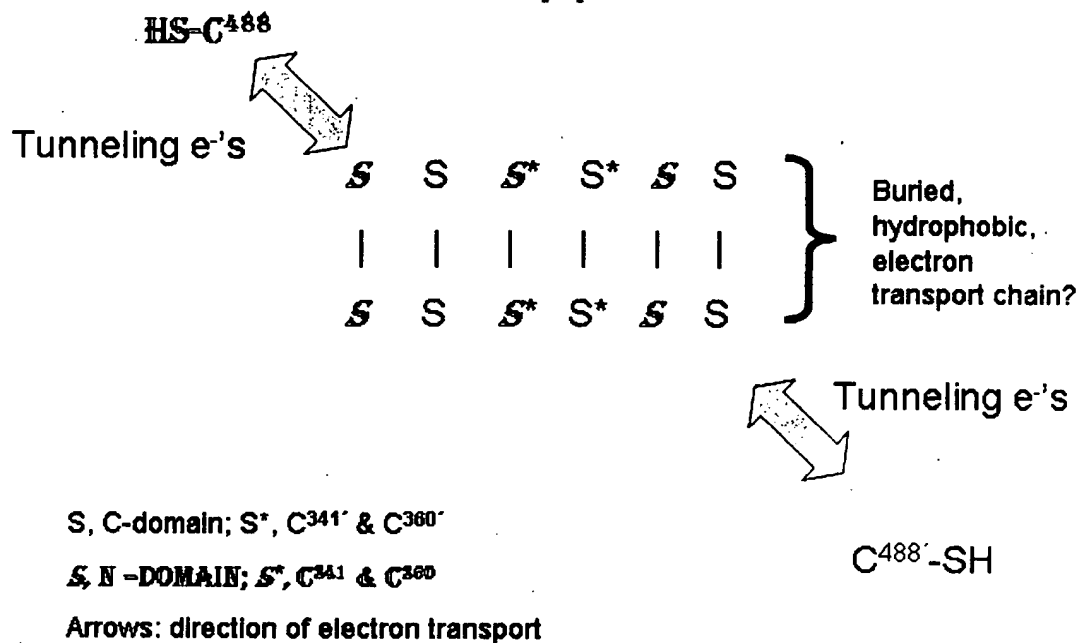
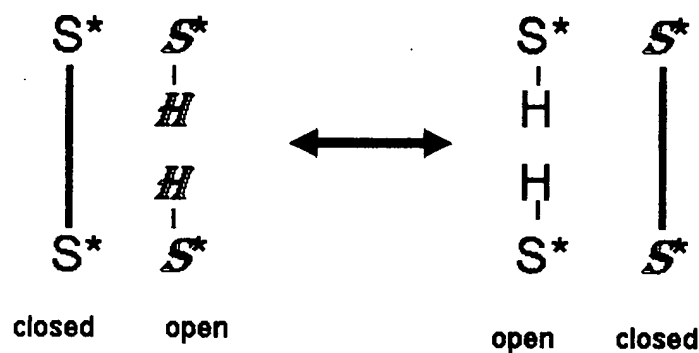


Figure 6. The disulfide isomerase exchange reaction possible at the heart of the disulfide zipper which might convert sACE into a kind of "reciprocating" enzyme.

sACE: a reciprocating enzyme with higher k_{cat} than tACE?

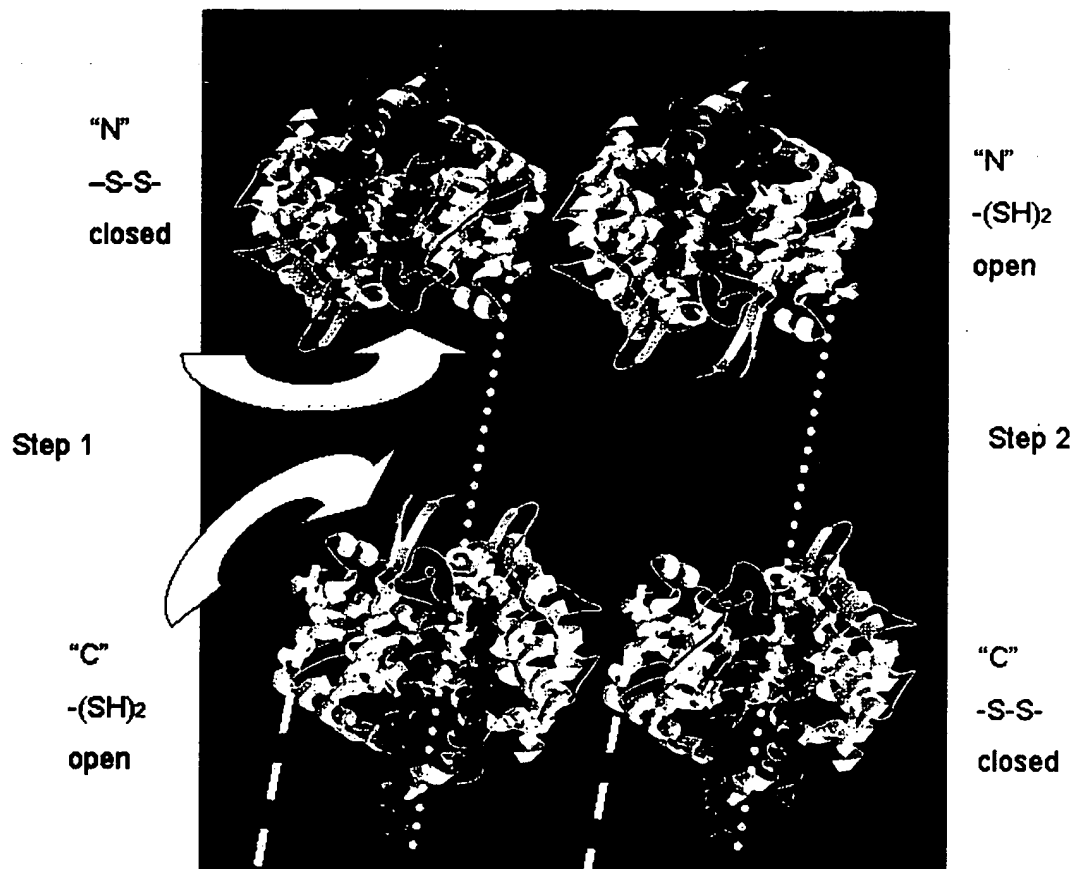


Activated by a single pair of electrons

S^* , C-domain cysteine 341' or 360'

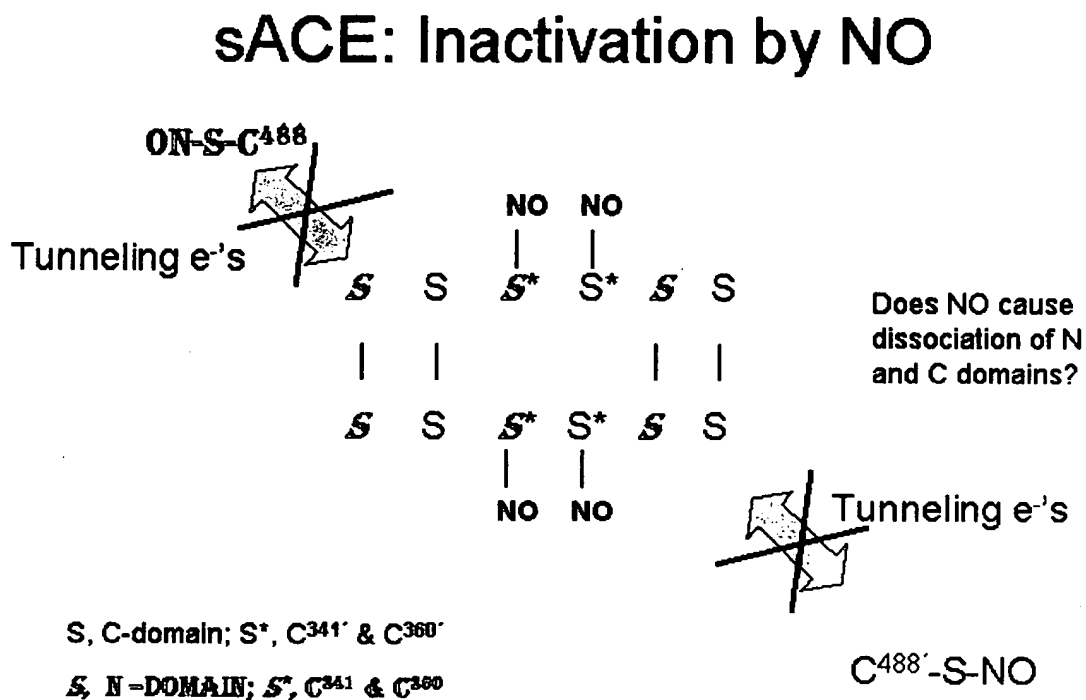
S^* , N-DOMAIN CYSTEINE 341 OR 360

Figure 7. The two steps in the catalytic cycle of the "reciprocating" enzyme, sACE.



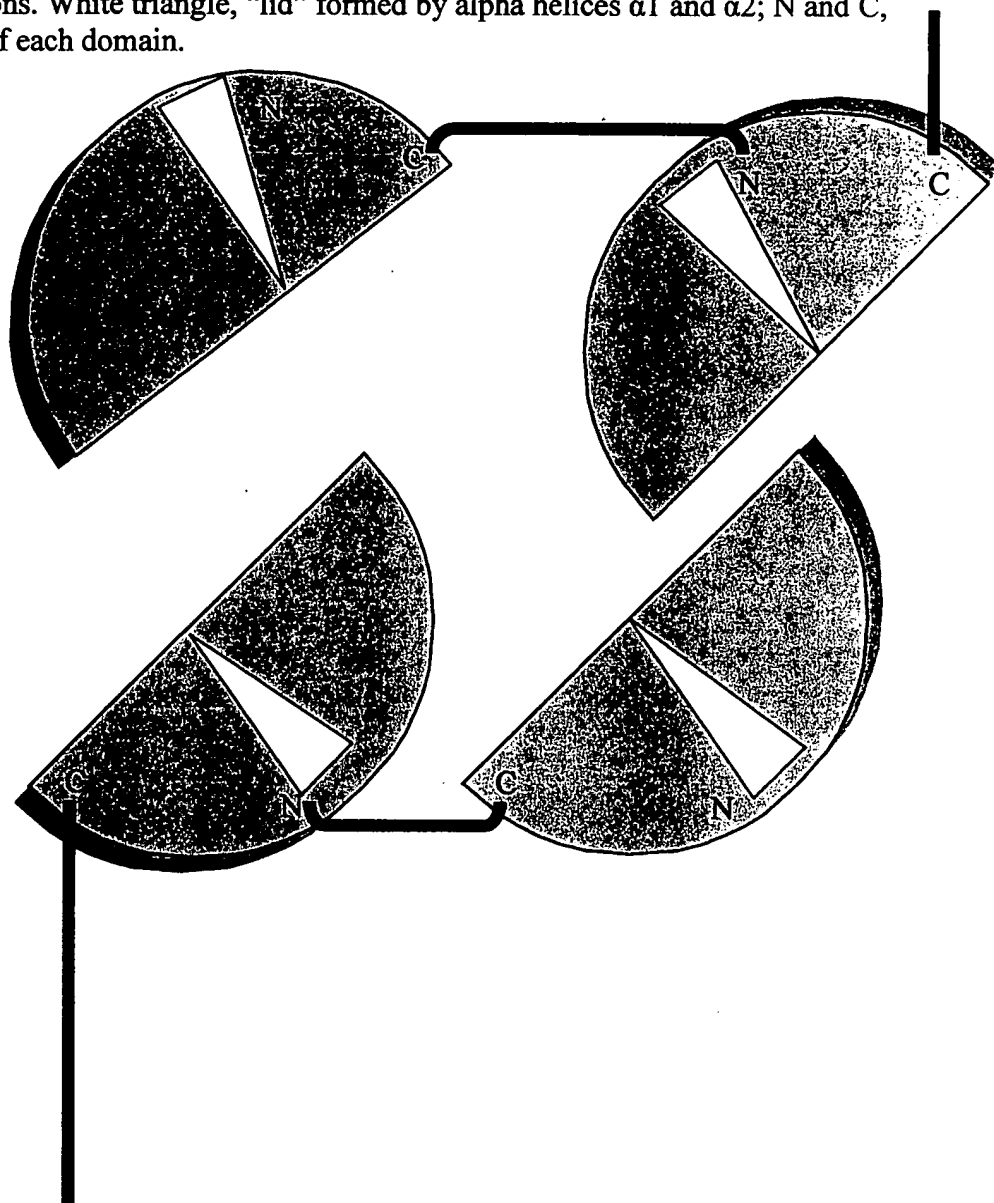
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Figure 9. NO inactivation of sACE: possible sites of S-nitrosylation.



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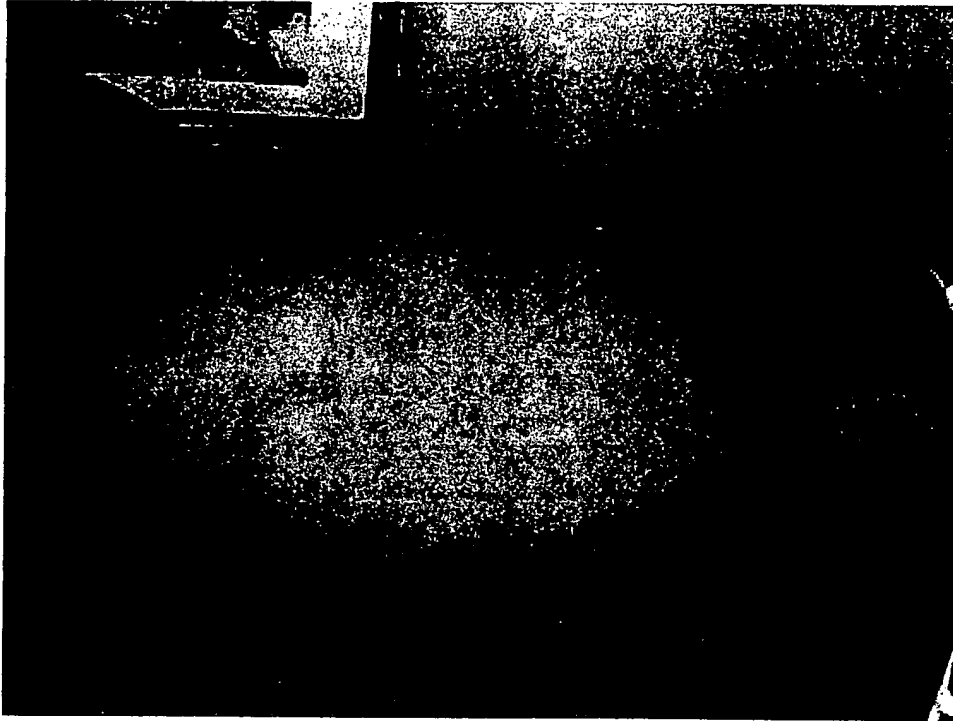
Figure 10. sACE on one immunocyte (T cell, monocyte/macrophage, or endothelial cell) binding to sACE on another immunocyte so as to promote specific cell-cell interactions. White triangle, "lid" formed by alpha helices $\alpha 1$ and $\alpha 2$; N and C, termini of each domain.



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Figure 11. Prompt response to angiotensin II receptor blockade in a 33 yr old white man with psoriasis. a,b,c: back and nail before treatment; d,e,f: 3 weeks after taking valsartan 80 mg daily. In a second case, a 62 yr old white man with chronic psoriasis, for which he took 75 mg methotrexate daily, was able to stop his methotrexate within 2 months of starting quinapril 200 mg/day.

a

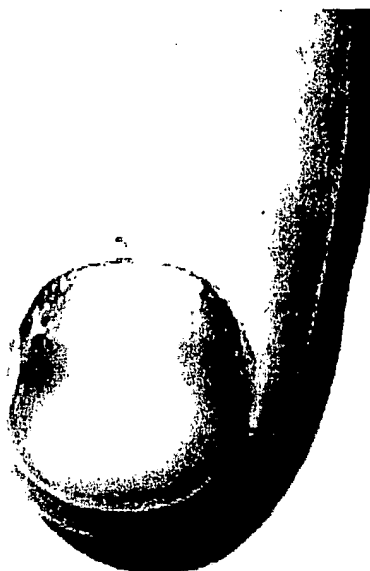


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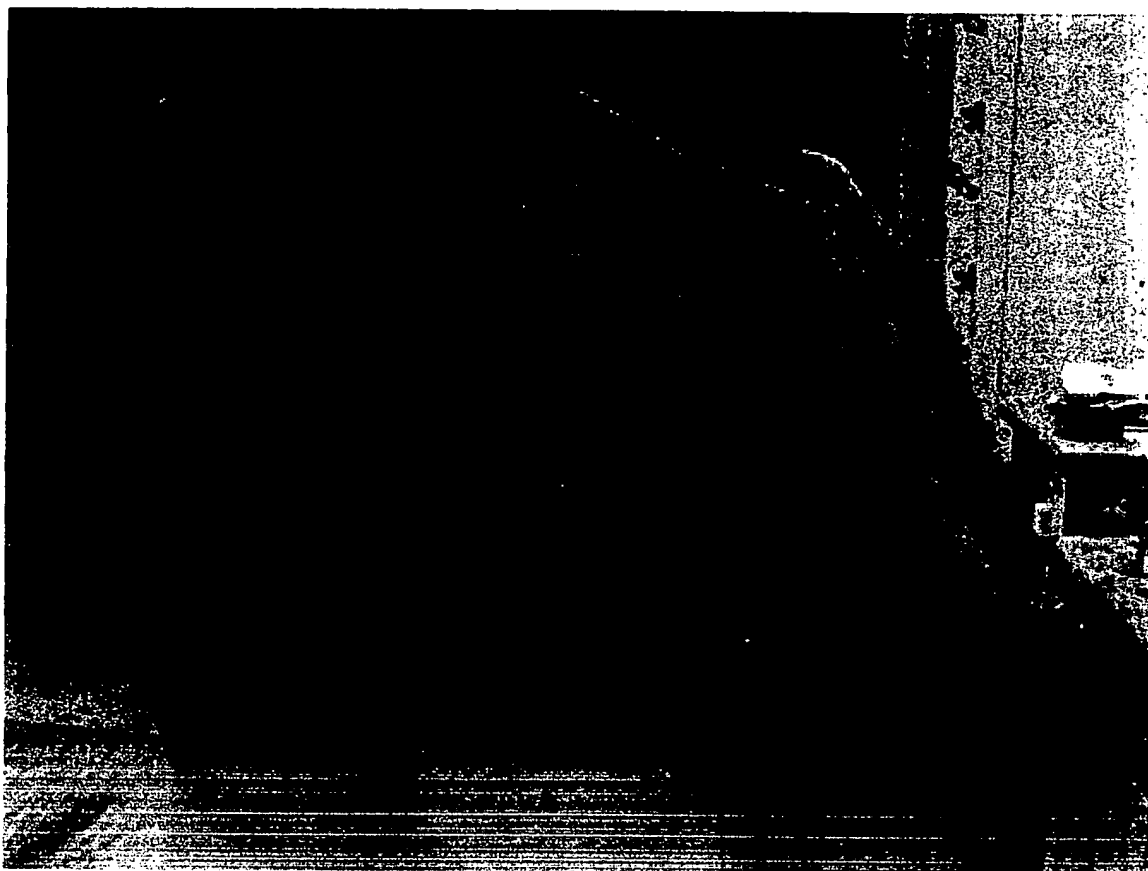


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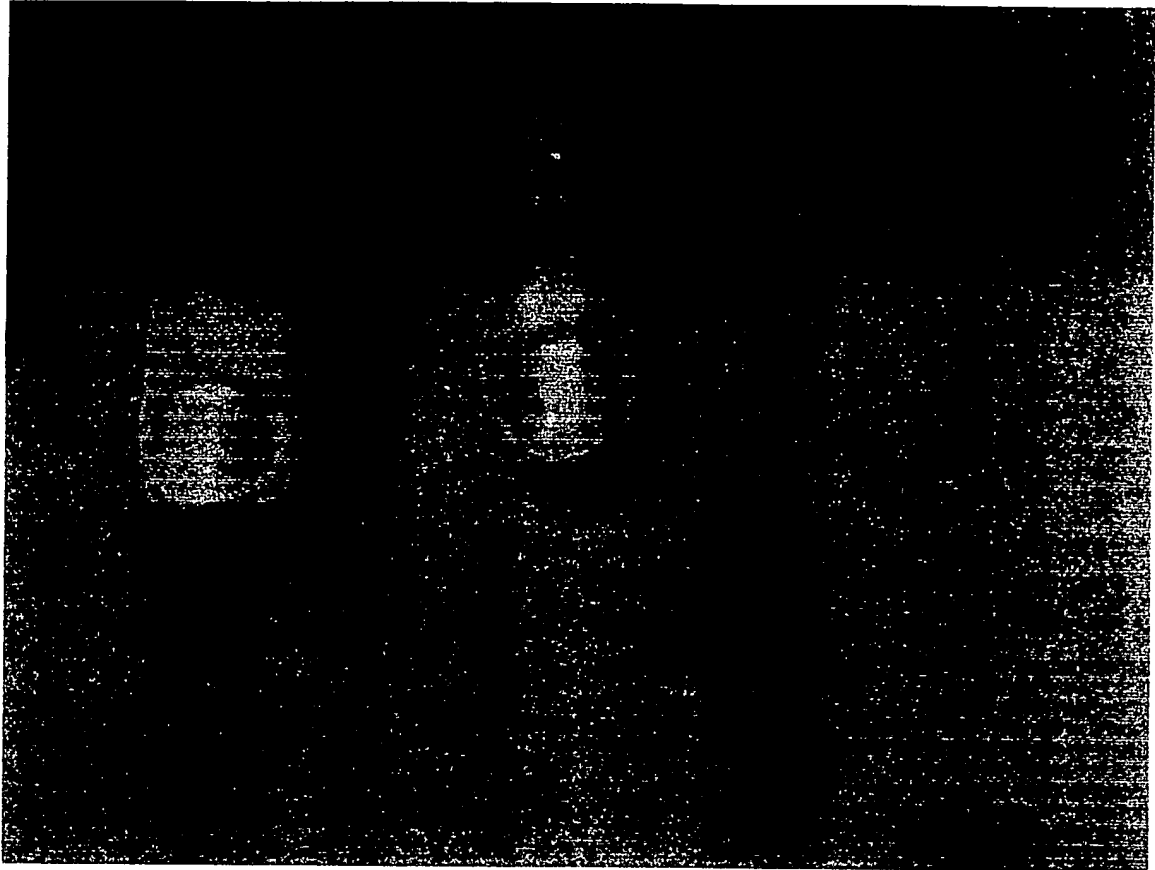
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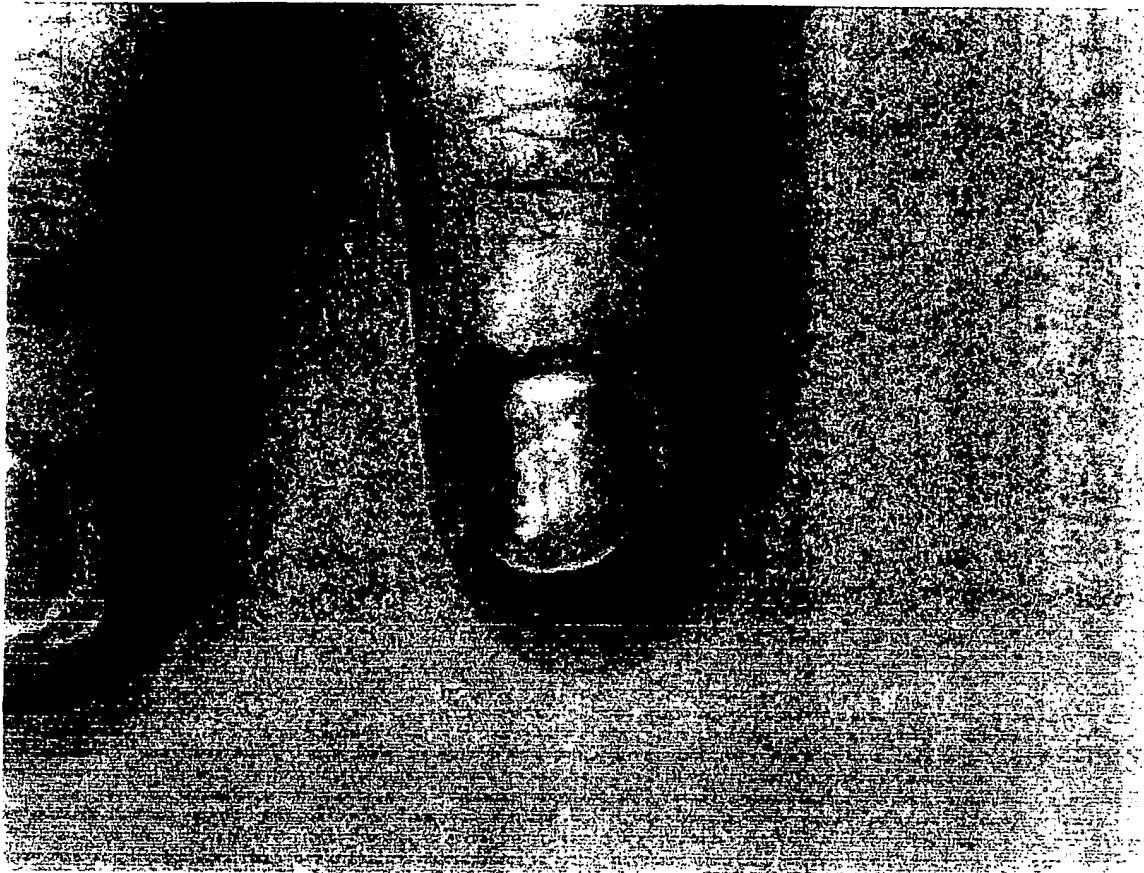
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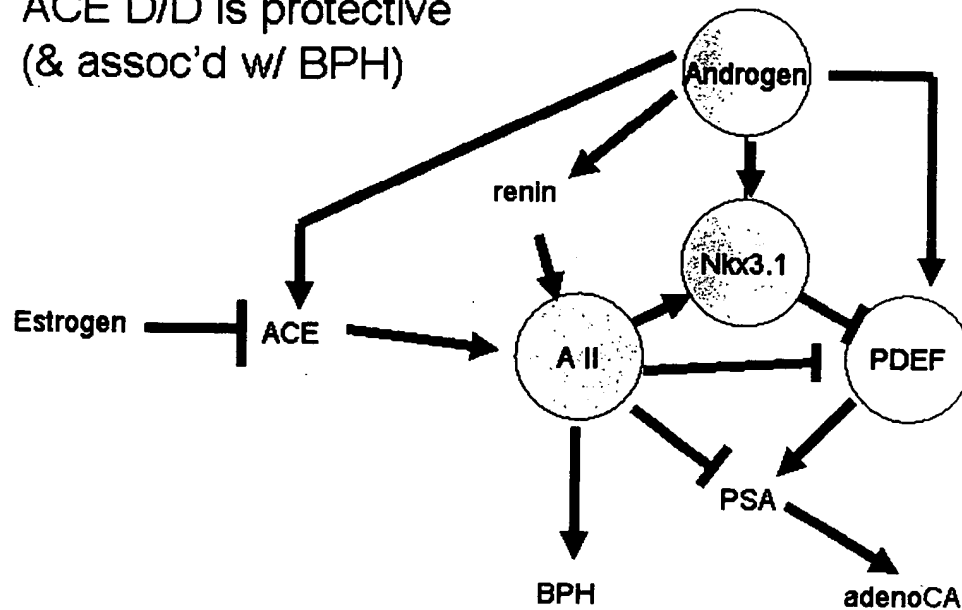


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Figure 12. Genetic pathway for initiation of benign prostatic hyperplasia and prostate cancer. PDEF, prostate-derived ets factor.

Prostate Cancer in White Men

- ACE D/D is protective (& assoc'd w/ BPH)



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